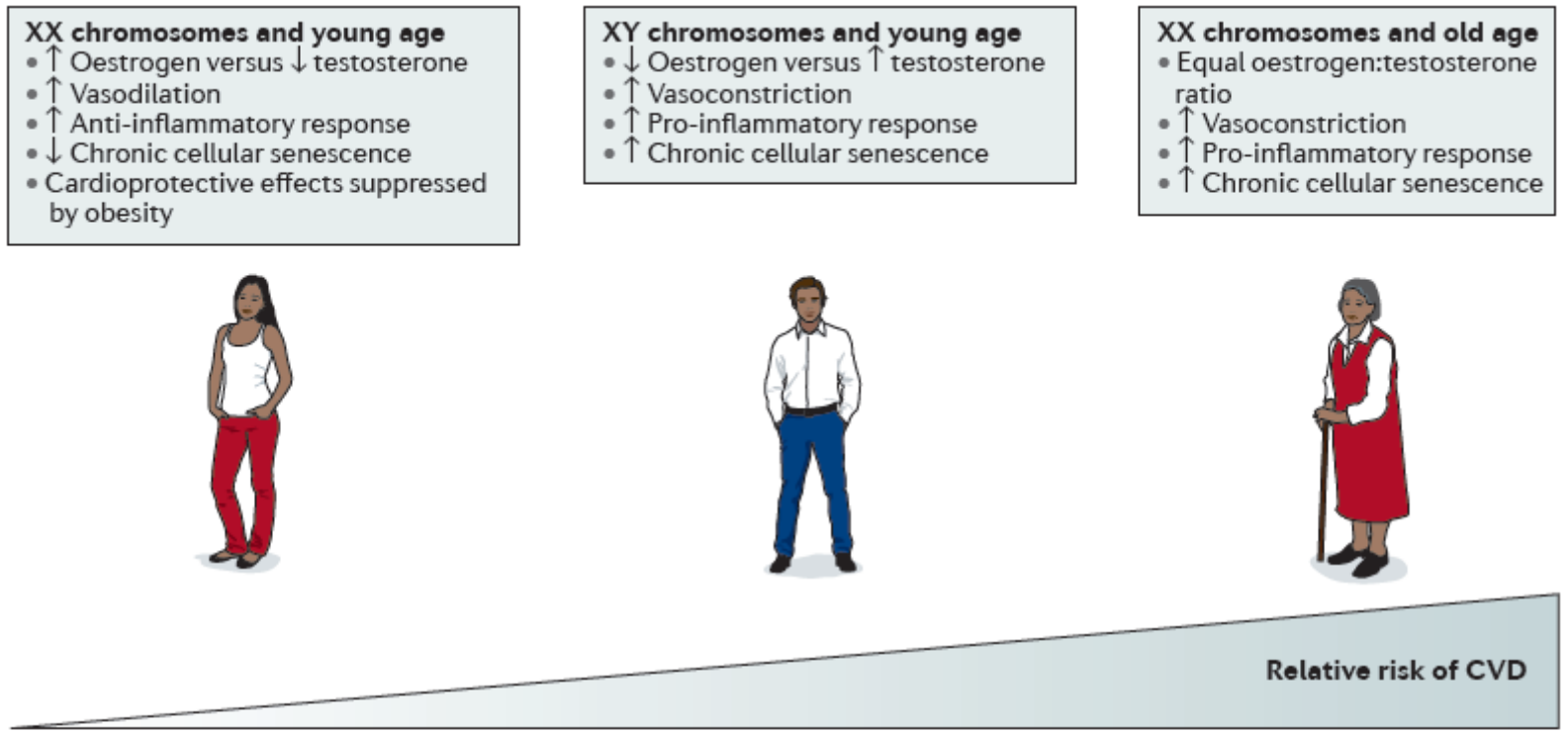
Sex-specific differences in hypertension and associated vascular disease

Hypertension

Hypertension has traditionally been defined as BP ≥140/90 mmHg, but 2017 guidelines have lowered the threshold to ≥130/80 mmHg

- The prevalence of hypertension as well as cardiovascular and renal diseases is lower in premenopausal women than in age-matched men and postmenopausal women, and these differences are seen across different ethnic populations.
- This cardio-renal protection is lost postmenopause: the incidence of hypertension in postmenopausal women is fourfold higher than in premenopausal women, whereas the incidence in age-matched men increases only threefold.
- Hypertension is a major risk factor for cardiovascular disease (CVD), which is the most common cause of death worldwide .
- premenopausal women have a lower incidence and severity of hypertension — and therefore a lower incidence of CVD — than men, the risk increases sharply after menopause


XX chromosomes and young age
• ↑ Oestrogen versus ↓ testosterone
• ↑ Vasodilation
• ↑ Anti-inflammatory response
• ↓ Chronic cellular senescence
• Cardioprotective effects suppressed by obesity
XY chromosomes and young age
• ↓ Oestrogen versus ↑ testosterone
• ↑ Vasoconstriction
• ↑ Pro-inflammatory response
• ↑ Chronic cellular senescence
XX chromosomes and old age
• Equal oestrogen:testosterone ratio
• ↑ Vasoconstriction
• ↑ Pro-inflammatory response
• ↑ Chronic cellular senescence
Relative risk of CVD

b

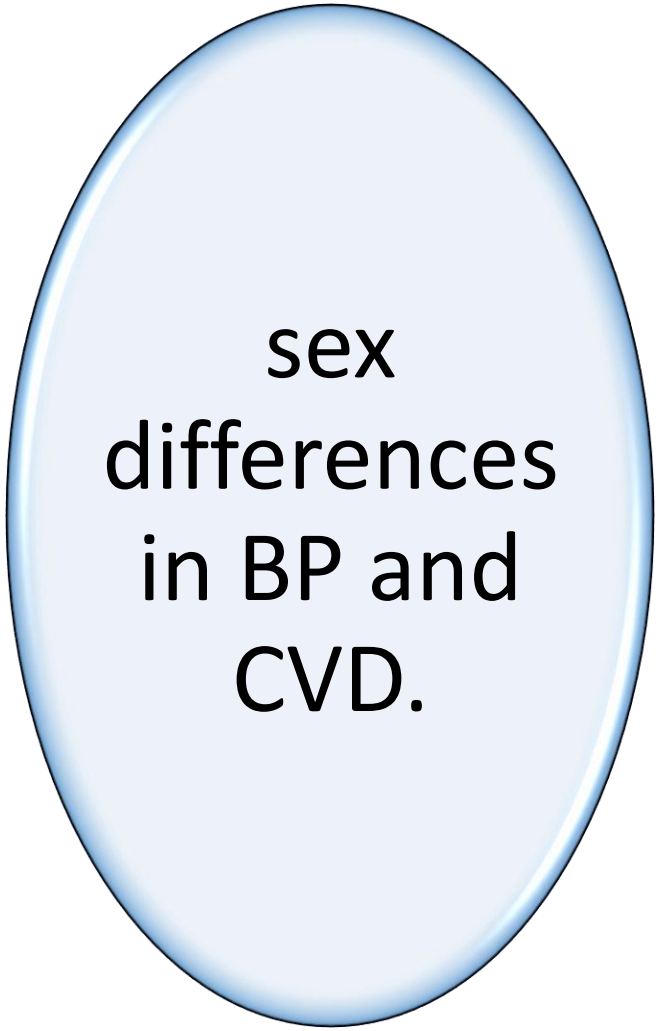

Factors promoting vasodilation:
• Oestrogen (?)
• Testosterone
• Y chromosome
• Progesterone
• Relaxin (in female mice)
• Oxytocin (in male rats)
• Short-term high-fat diet (females)
Depressor pathways
Pressor pathways
Factors promoting vasoconstriction:
• Testosterone
• Y chromosome
• Inflammatory response
• Obesity
• Vasopressin
• Progesterone

The factors probably has a major role in sexual dimorphism relating to BP regulation and cardiovascular function

- ***Renal function***
- ***Cellular senescence***
- **Immune system**
- **Sex hormones**
- **Sex chromosome**
- **Lifestyle and environmental factors**

Key systems that are important in the development of hypertension and cardiovascular disease (CVD) :

- Sympathetic nervous system
- Renin–angiotensin–aldosterone system
- Immune system



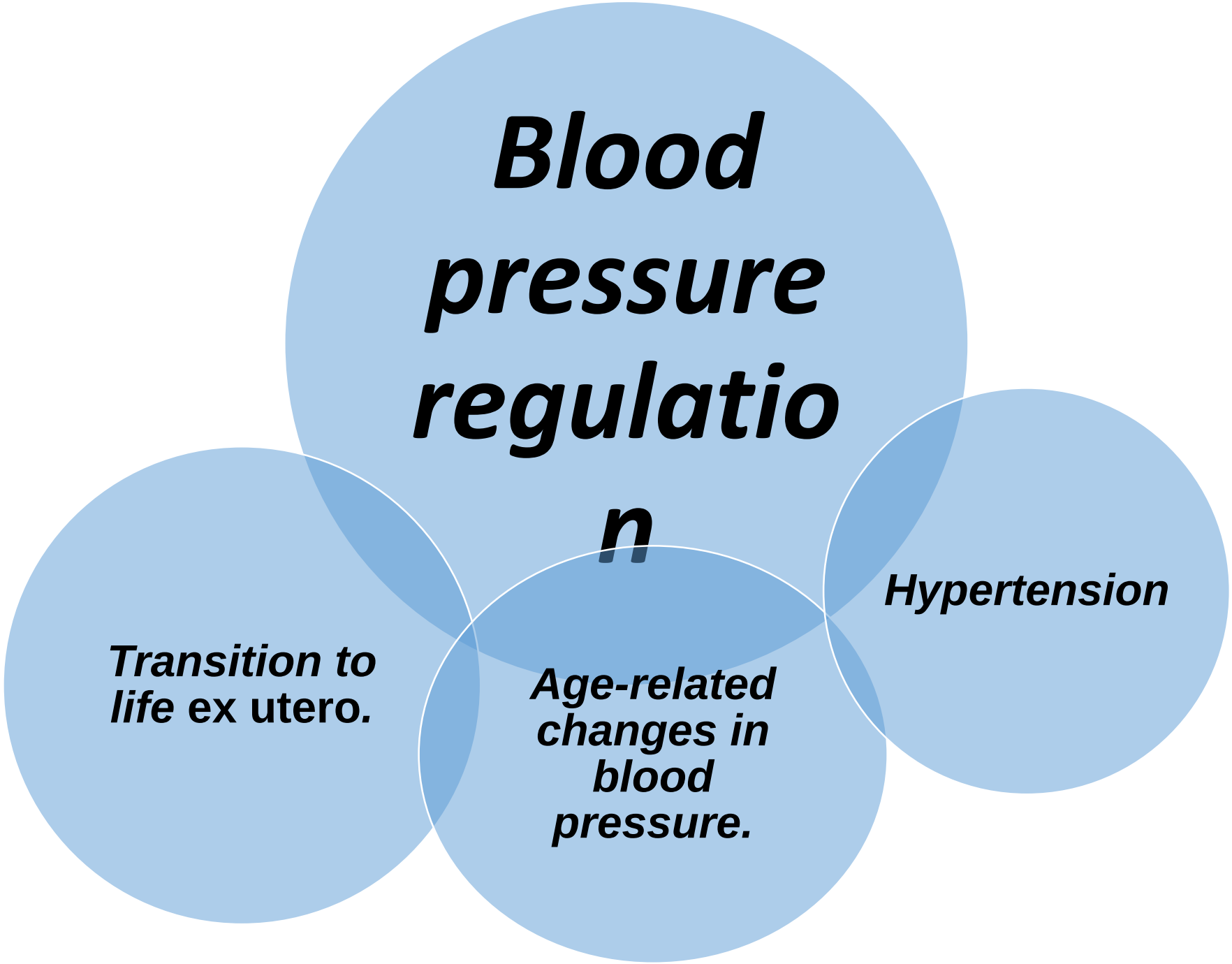
Biological age

- Women have a longer lifespan than men — living 5 years longer on average

- Biological age probably has a major role in sexual dimorphism relating to BP regulation and cardiovascular function, which contributes to sex differences in cardiovascular risk.

Table 1 | **Effects of sex and age on arterial blood pressure in humans**

Study (year)	Study (year)	BP values*							
		Male				Female			
		6–11 years	12–17 years	18–55 years	>55 years	6–11 years	12–17 years	18–55 years	>55 years
Kwok *et al.* (2014)	Follow-up of Hong Kong's 'Children of 1997' birth cohort (China); healthy, *n* = 6,276 at ~11 years and *n* = 5,305 at ~13 years; 48% female	102/58	111/61	NA	NA	102/58	107/61	NA	NA
Williams and Poulton (2002)	Follow-up of the Dunedin Multidisciplinary Heath and Development Study 1972–1973 cohort (New Zealand); healthy, *n* = ~375 males and ~345 females	105/65	114/58	124/65	NA	104/65	111/59	113/63	NA
Shen *et al.* (2017)	The Bogalusa Heart Study (1973–2010): a longitudinal follow-up in populations of different ethnic origin (black and white; USA); healthy, *n* = 960 black and 1,772 white; 55% female	• 100/61 • 100/60	• 112/67 • 115/69	• 120/81 • 126/83	NA	• 100/62 • 100/60	• 109/70 • 111/70	• 113/75 • 123/81	NA
Roberts *et al.* (1977)	NHANES I (1971–1974) cross section of the general population aged 6–74 years (USA); healthy, *n* = 6,768; 50% female	103/65	115/71	128/83	143/86	103/64	112/69	122/78	148/86
Drizd *et al.* (1986)	NHANES II (1976–1980) cross section of the general population aged 18–74 years (USA); healthy, *n* = 12,504; ~50% female	NA	NA	127/81	140/84	NA	NA	118/76	142/82
Wiinberg *et al.* (1995)	Cross section of the general population aged 20–79 years (Denmark); healthy, *n* = 30 males and 30 females at each age	NA	NA	125/76	136/80	NA	NA	113/74	129/77

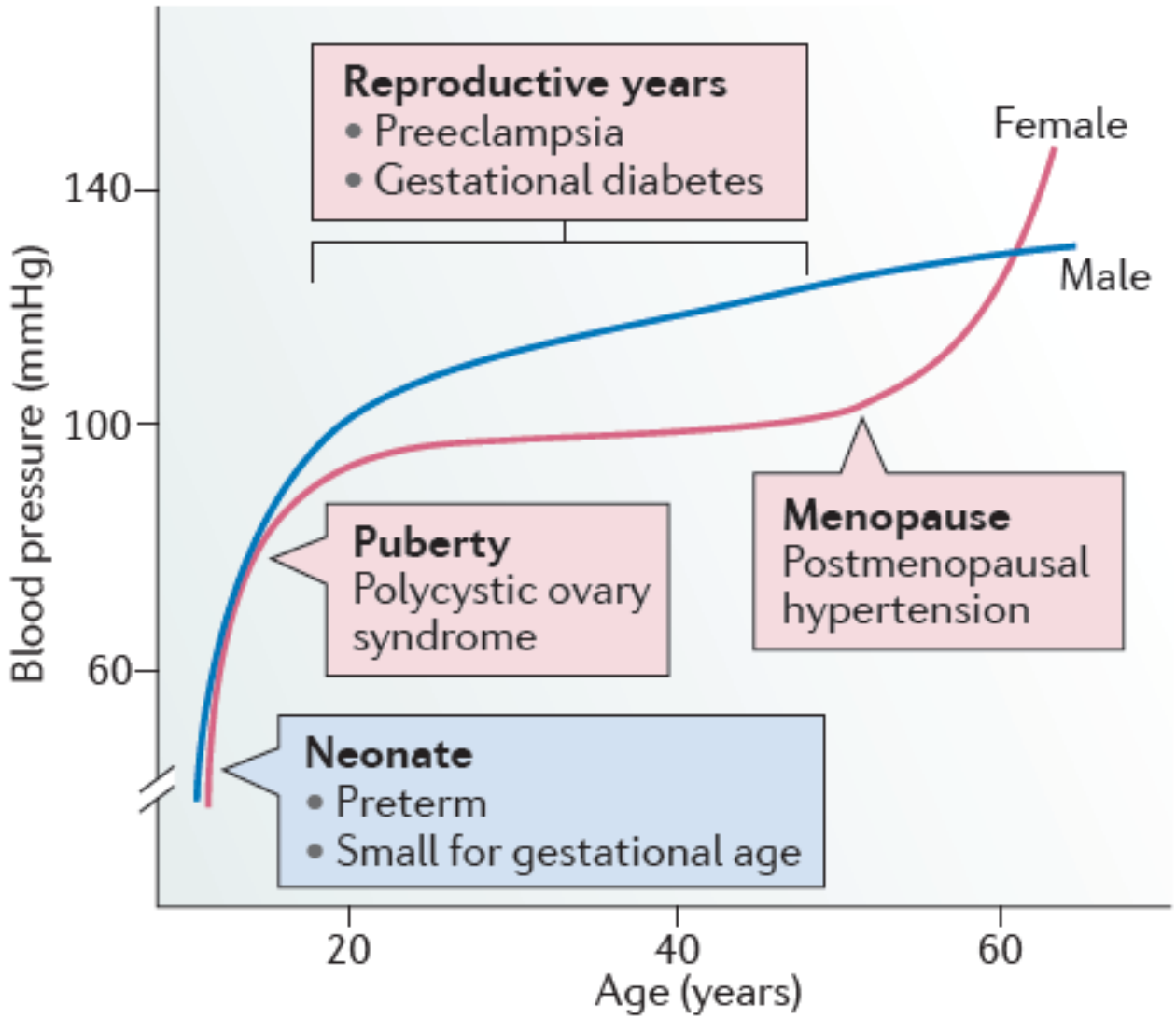

Blood pressure regulation
Transition to life ex utero.
Age-related changes in blood pressure.
Hypertension

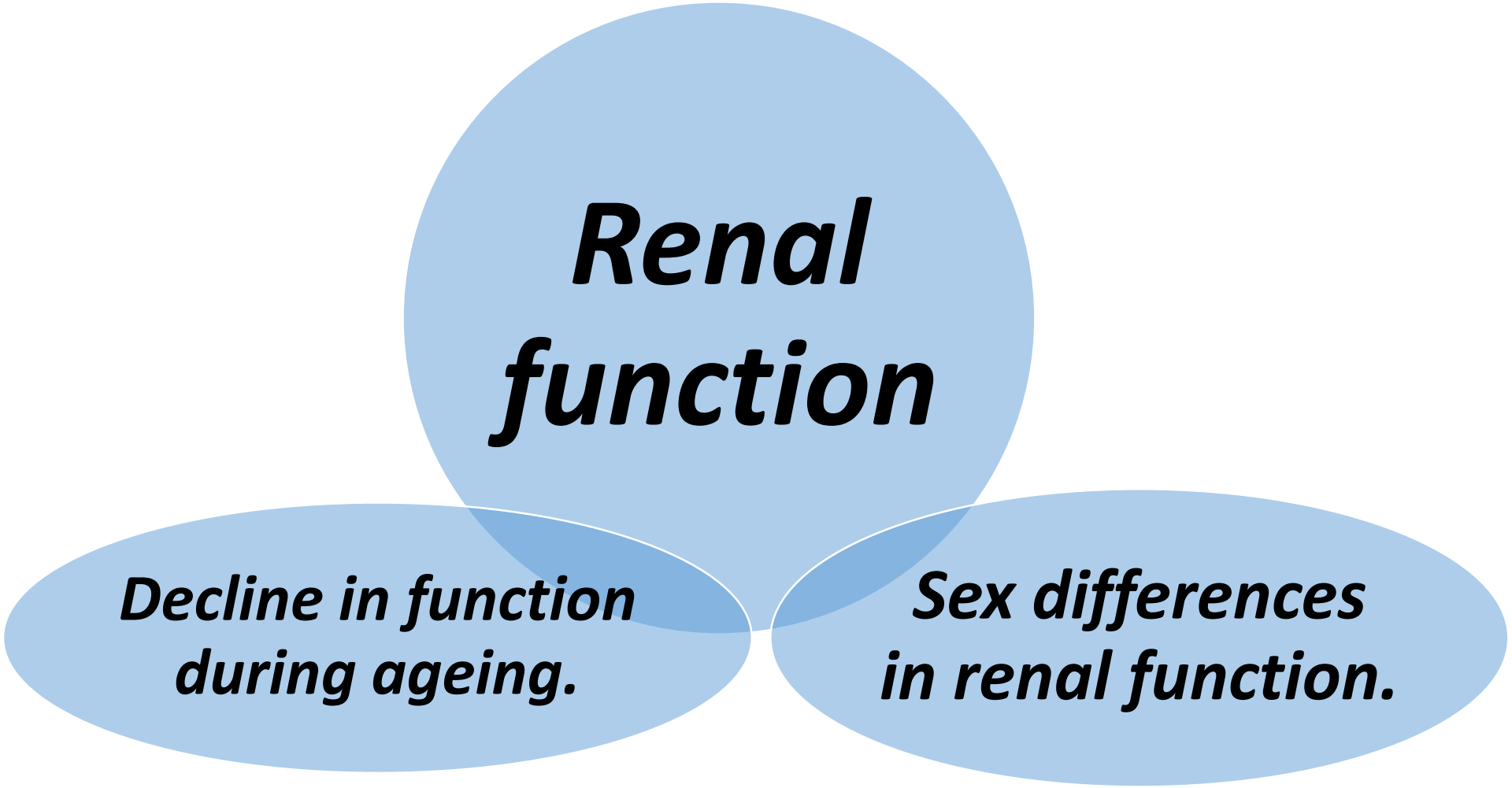
Age-related changes in blood pressure.

- Arterial BP increases with age in mammals, including humans.
- At birth, BP is low (40–50 mmHg) and rises steadily until adolescence, at which point BP values diverge in males and females. In males, BP continues to rise, increasing approximately 25 mmHg from 10 to 40 years of age, but in females, the rise in BP over the same period is only ~15 mmHg
- from ~60 years of age, BP starts to rise steeply in women and eventually surpasses that of age-matched men.
- This cardio-renal protection is lost postmenopause

- Loss of cardio-renal protective mechanisms with age may also contribute to the sharp increase in hypertension and CVD in postmenopausal women.

- Defects in these protective pathways may contribute to the development of vascular diseases that are unique to younger premenopausal women (such as hypertensive disorders of pregnancy, gestational diabetes, polycystic ovary syndrome (PCOS) and hypothalamic hypoestrogenaemia).


Reproductive years
• Preeclampsia
• Gestational diabetes
Female
Male
140
100
60
Blood pressure (mmHg)
Puberty
Polycystic ovary syndrome
Menopause
Postmenopausal hypertension
Neonate
• Preterm
• Small for gestational age
20
40
60
Age (years)


Renal function
Decline in function during ageing.
Sex differences in renal function.

Decline in function during ageing:

As the kidney plays a key part in the determination of BP, loss of renal function with age or disease can drive an increase in BP.

Ageing is associated with renal structural alterations, including reduced cortical mass owing to :

- Tubular atrophy
- interstitial fibrosis
- glomerular sclerosis
- a functional decline in glomerular filtration rate (GFR)

- Which decreases by ~10% for every decade of life after the age of 30 years in humans.

- This reduction in renal function with age is associated with a loss of nephrons, which likely contributes to the twofold higher prevalence of chronic kidney disease among people aged >60 years than among those <60 years of age

Sex differences in renal function

Sex differences in renal function exist, particularly in regard to mechanisms of salt and water handling :

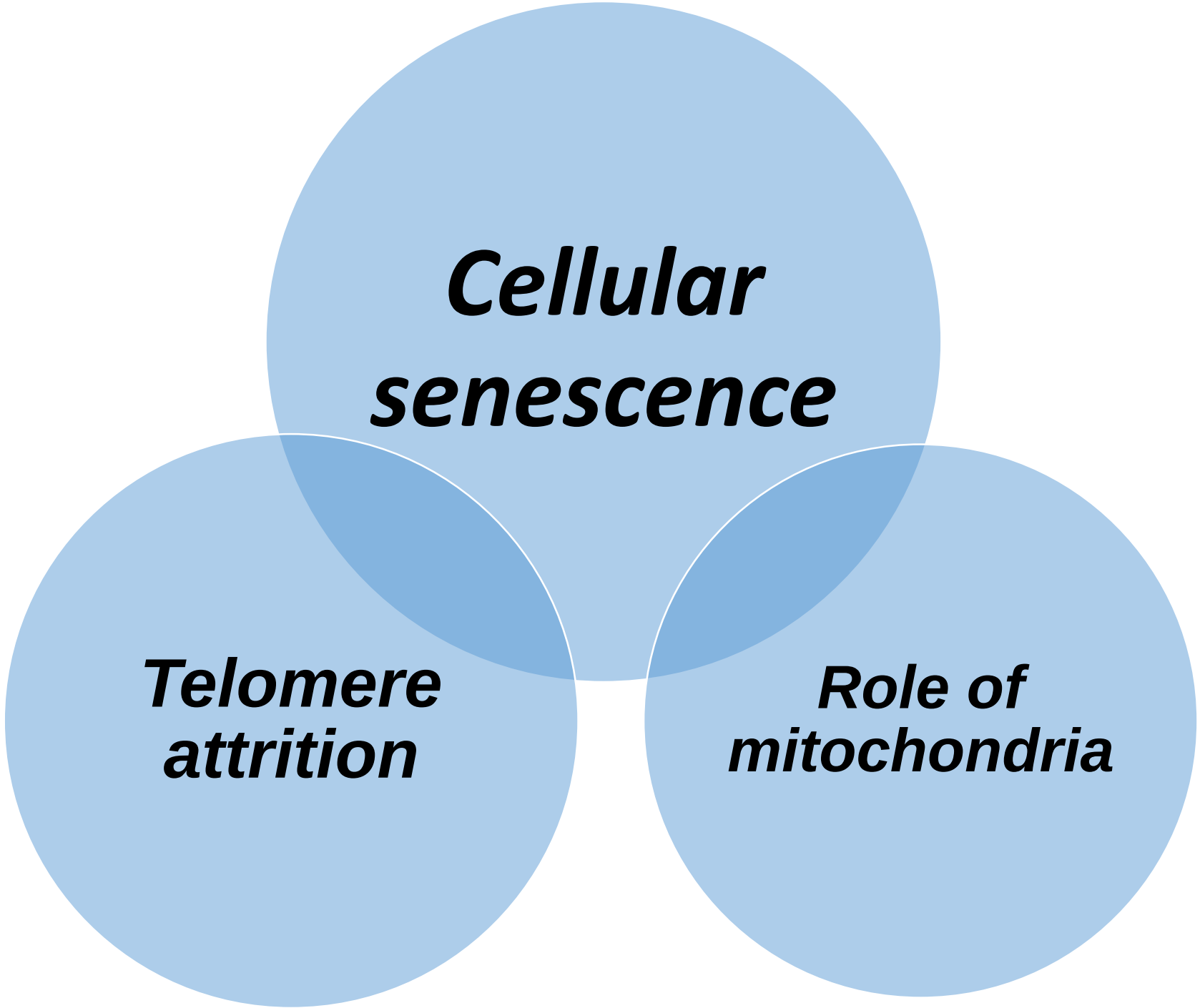
- females excrete the same amount of sodium at a lower arterial pressure than males
- This greater ability to excrete sodium likely contributes to the lower basal BP (~5–10 mmHg) in female than in male adult
- BP is more salt-sensitive in aged than in adult female, as characterized by a rightward shift in the pressure–natriuresis relationship.

Mirabito, K. M. *et al.* Sex- and age-related differences in the chronic pressure-natriuresis relationship: role of the angiotensin type 2 receptor. *Am. J. Physiol. Renal Physiol.* **307**, F901–F907 (2014).

Expression levels of sodium/hydrogen exchanger 3 (NHE3), the main transporter present in the proximal portion of the renal tubule, are lower in females than in males

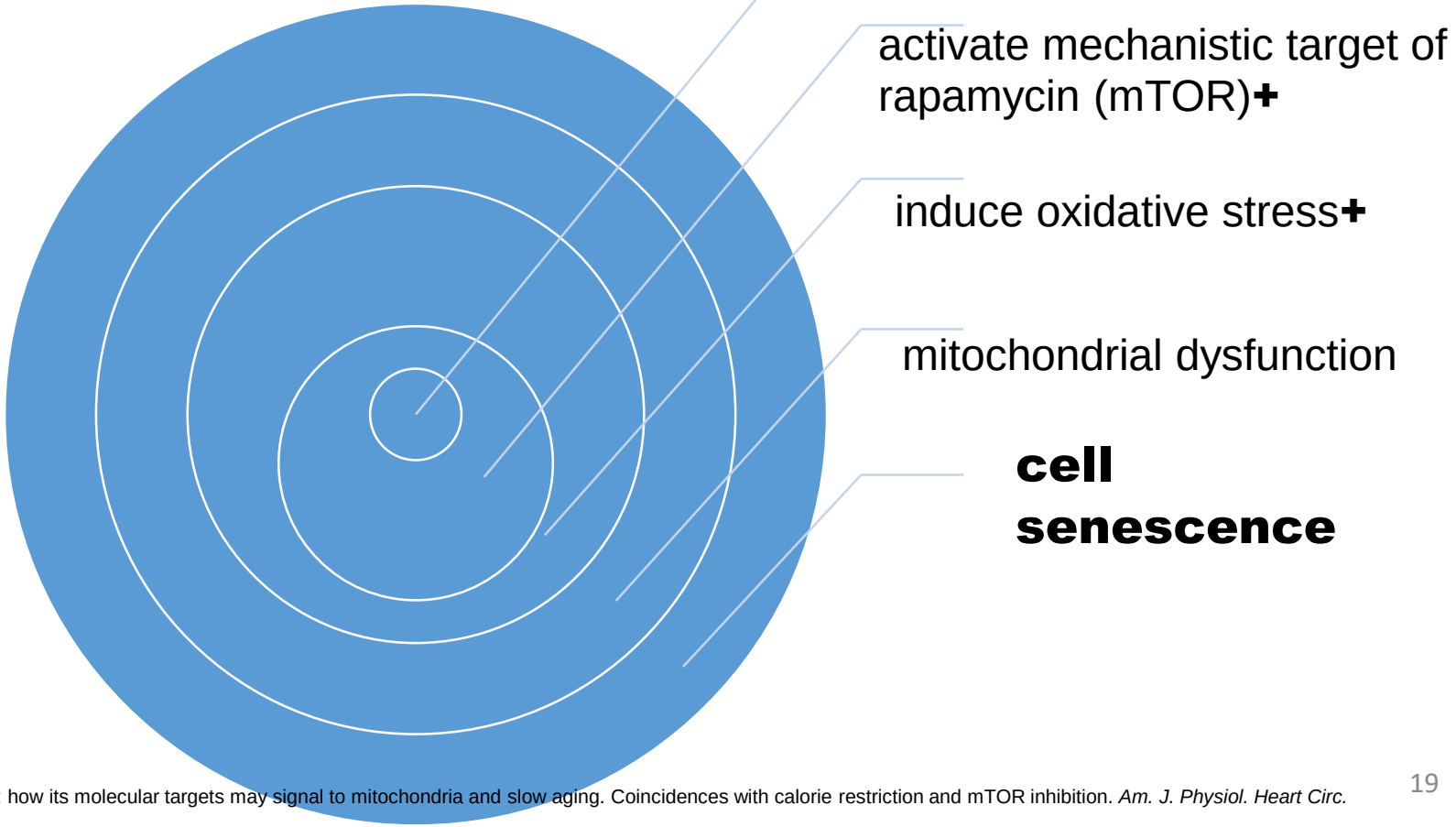
whereas in distal portions of the renal tubule, sodium/chloride co-transporter (NCC) and epithelial sodium channel (ENaC) abundance is greater in female than in males.

These differences may lead to reduced reabsorption in early segments of the tubule in females but increased reabsorption in the distal tubules and collecting duct, ultimately facilitating sodium excretion in females.


Cellular senescence
Telomere attrition
Role of mitochondria

- RAAS inhibition reduces the age-related loss of renal function by modulating senescence-associated pathways.

- age suppresses the systemic RAAS, but intrarenal sensitivity to angiotensin II is increased at least in males, which may promote renal cellular senescence.



de Cavanagh, E. M., Inserra, F. & Ferder, L. Angiotensin II blockade: how its molecular targets may signal to mitochondria and slow aging. Coincidences with calorie restriction and mTOR inhibition. *Am. J. Physiol. Heart Circ. Physiol.* **309**, H15–H44 (2015).

Telomere attrition

- Telomere length is similar in both sexes at birth but shortens more rapidly throughout life in men than women.
- Once telomere shortening reaches a critical level, telomeres can induce permanent cellular senescence.
- Mechanistic evidence suggests that increased renal oxidative stress drives telomere shortening and cellular senescence in male.
- telomere uncapping is twofold greater in arterial biopsy samples from subjects with hypertension.
- Greater telomere attrition in obese females may therefore contribute to the increased risk of CVD in this patient population.

- in postmenopausal women arterial telomere uncapping is 2.5-fold greater than that in premenopausal women , which has been associated with a greater expression of cellular markers of senescence

- telomere uncapping is twofold greater in arterial biopsy samples from subjects with hypertension

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PMID: 26602606

Age-related arterial telomere uncapping and senescence is greater in women compared with men

Ashley E Walker,[1] R Garrett Morgan,[1] Stephen J Ives,[1,2,3,4] Richard M Cawthon,[5] Robert H I Andtbacka,[6] Dirk Noyes,[6] Lisa A Lesniewski,[1,2,3] Russell S Richardson,[1,2,3] and Anthony J Donato[1,2,3]

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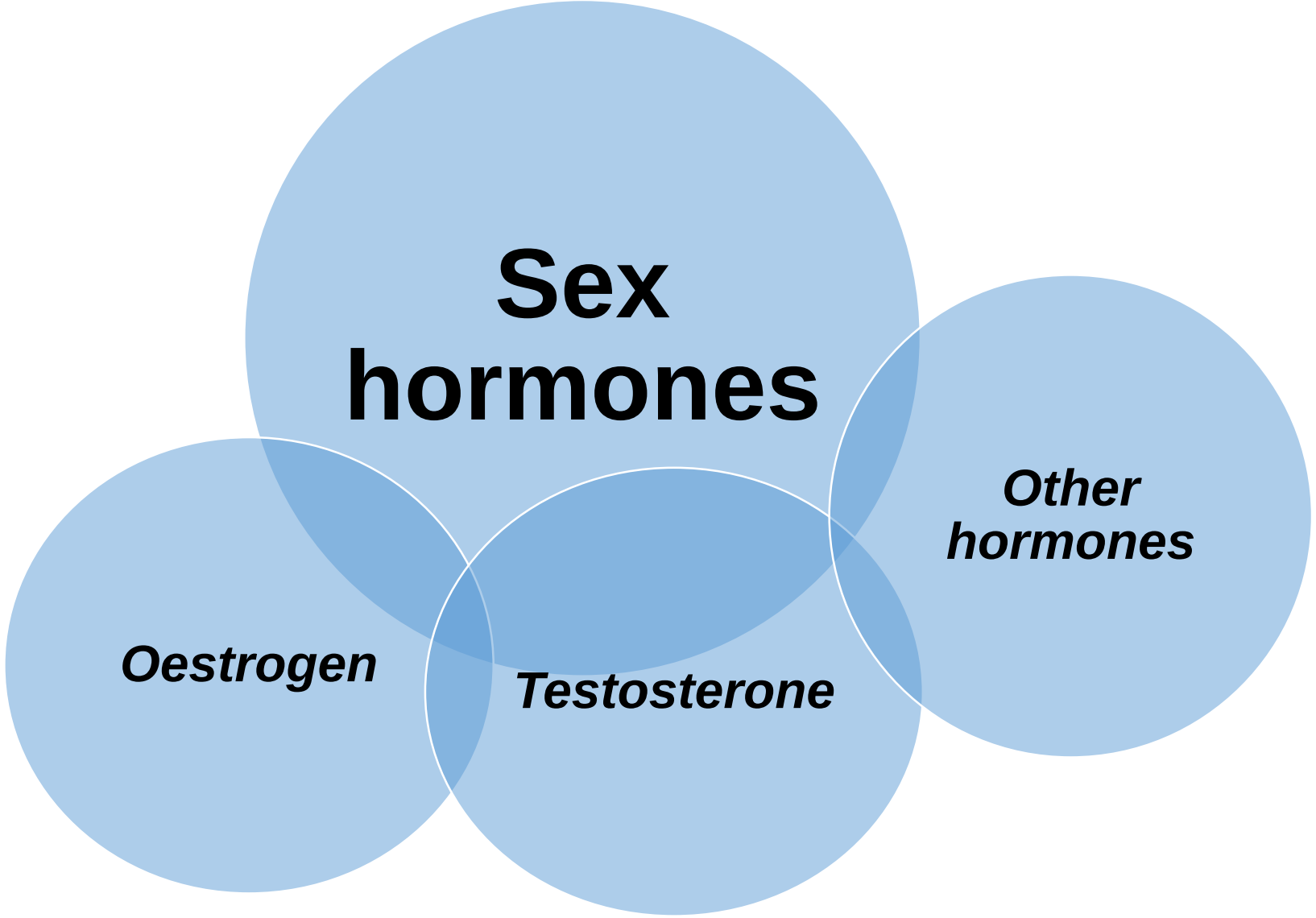
- Telomere shortening has also been linked to adiposity in humans, which is of particular interest given that obesity has increased deleterious effects on cardiovascular health in women compared with men

Role of mitochondria.

- Mitochondrial dysfunction has become an area of intense interest with regard to its role in the pathophysiology of CVD and ageing.

- mitochondrial DNA is exclusively inherited from the mother, which likely contributes to sex differences in lifespan owing to greater penetrance of mutations in males, resulting in sub-optimal mitochondrial function

- Marked sex differences in mitochondrial function have been reported that could contribute not only to the increased longevity of women but also to cardioprotection


Sex hormones
Oestrogen
Testosterone
Other hormones

Oestrogen

- oestrogen increases the synthesis of angiotensinogen and decreases the synthesis of the RAAS enzymes renin and ACE
- oestrogen is associated with lower BP in women
- Oestrogen modulates the expression of most components of the RAAS, shifting the balance towards the so-called protective depressor RAAS pathways
- oestrogen decreases the pro-hypertensive effects of ET1 by modulating not only the production of ET1 but also the expression of the endothelin receptor type A (ETAR) and endothelin receptor type B receptor (ETBR)

Oestrogen modulated BP

Directly: through non-genomic effects on vascular, renal and cardiac cells by reducing calcium efflux

Indirectly: through genomic actions, inhibiting the synthesis of potent vasoconstrictors, such as angiotensin II, endothelin 1 (ET1; also known as EDN1) and catecholamines

- BP is lower in women during the luteal phase — when high oestrogen levels are maintained — than during the follicular phase of the menstrual cycle

- hormonal changes during the luteal phase of the menstrual cycle are associated with increased arterial compliance, reduced endothelial reactivity, increased vascular smooth muscle cell sensitivity to nitric oxide and activation of the RAAS and endothelin system

- oestrogen also contributes to cardiovascular health in males

- important role for oestrogen in glucose and lipid metabolism

- oestrogen to influence immune cell function and inflammation, which may also confer cardiovascular protection

Testosterone

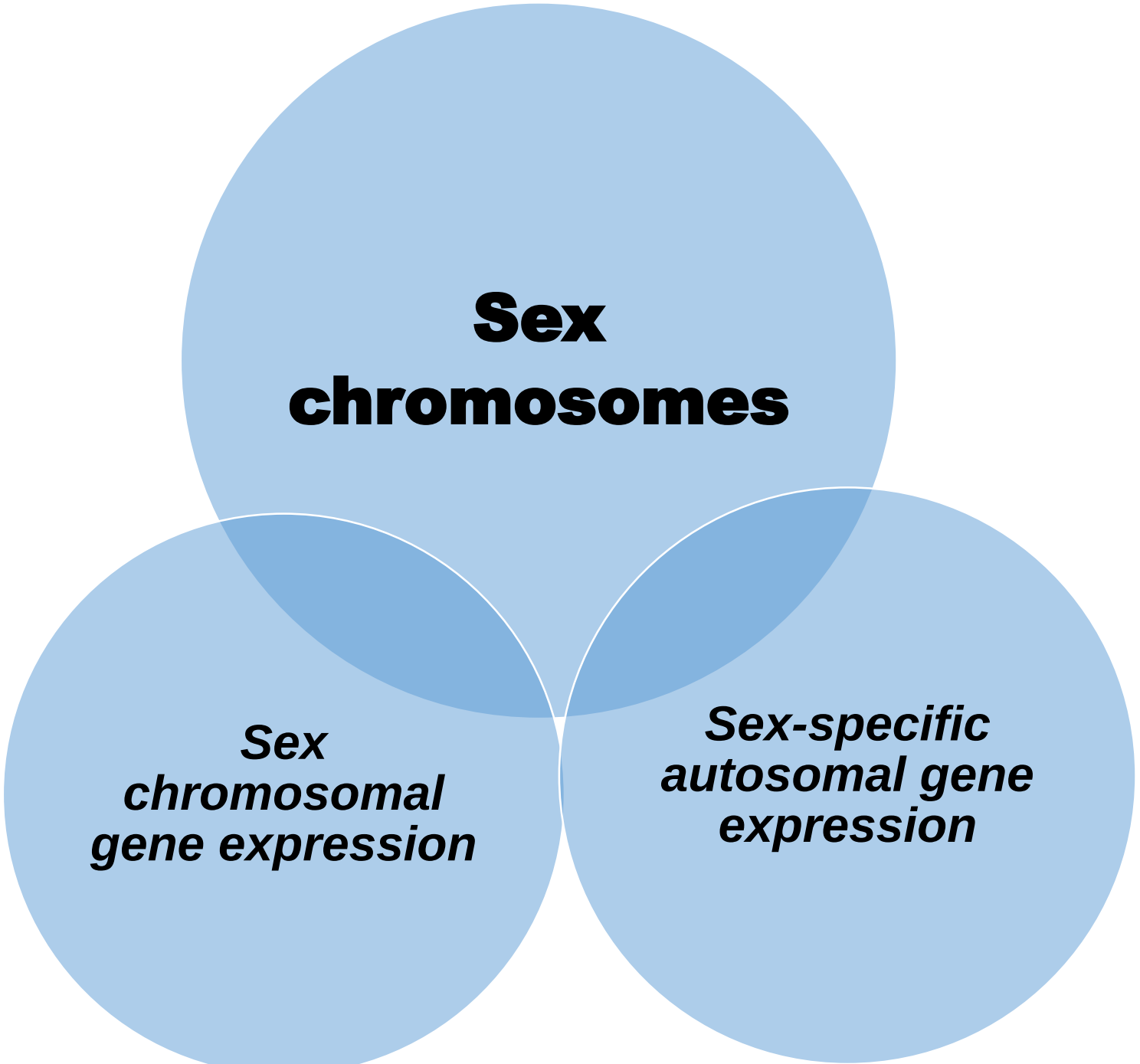
- testosterone is pro-hypertensive and likely contributes to the increase in cardiovascular risk observed with increasing age in males.

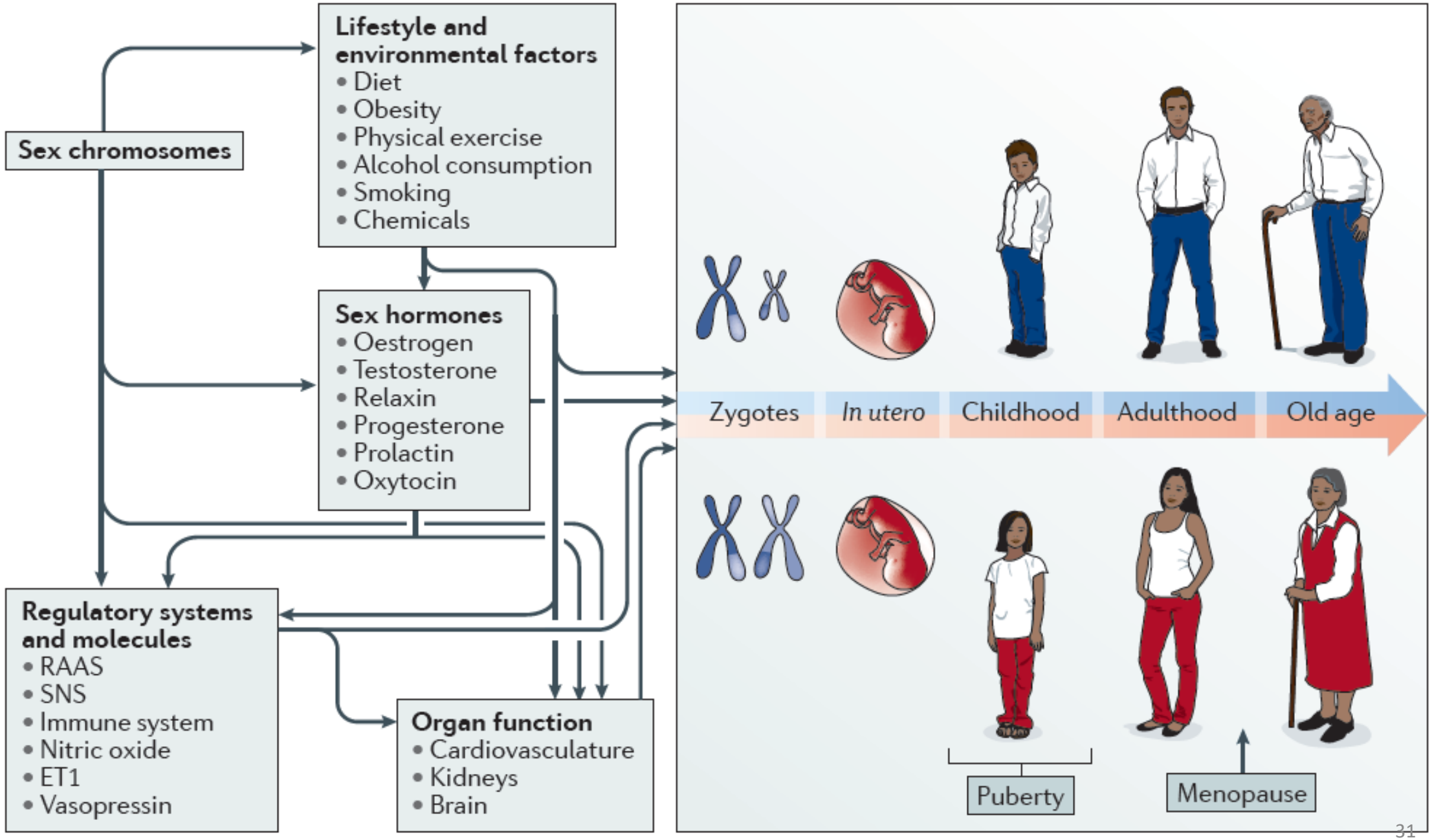
- testosterone can stimulate both vasodilatory and vasoconstrictor pathways.
- testosterone is associated with activation of AT1R, resulting in increased vasoconstriction, sodium retention by the kidneys and vascular and cardiac hypertrophy.

- plasma testosterone levels are elevated approximately twofold to threefold in women with PCOS — individuals who are at increased risk of developing vascular dysfunction and hypertension

Other hormones

- Relaxin has vasodilatory and anti-fibrotic functions in both sexes, and these effects may be increased in females
- oxytocin has also been shown to cause vasodilation and reduce BP in male, but this has not been investigated in females
- prolactin levels elevation have been associated with endothelial dysfunction and increased vascular stiffness in postmenopausal women
- Vasopressin (also known as anti-diuretic hormone) plays a major part in water homeostasis and is a potent vasoconstrictor. Levels of plasma vasopressin are higher in male than in female, resulting in greater decreases in urine flow and free water clearance and an increase in urine osmolality in males


Sex chromosomes
Sex chromosomal gene expression
Sex-specific autosomal gene expression


Lifestyle and environmental factors
• Diet
• Obesity
• Physical exercise
• Alcohol consumption
• Smoking
• Chemicals
Sex chromosomes
Sex hormones
• Oestrogen
• Testosterone
• Relaxin
• Progesterone
• Prolactin
• Oxytocin
Regulatory systems and molecules
• RAAS
• SNS
• Immune system
• Nitric oxide
• ET1
• Vasopressin
Organ function
• Cardiovasculature
• Kidneys
• Brain
Zygotes
In utero
Childhood
Adulthood
Old age
Puberty
Menopause

Sex chromosomal gene expression

Sex chromosomes contribute to the :

- Angiotensin II-mediated pressor response
- The development and progression of abdominal aneurysm
- Ischaemia–reperfusion injury in the heart and atherosclerosis

- The sex chromosomes can cause sex differences in non-gonadal tissues independent of the effects of gonadal hormones

Alsiraj, Y. *et al.* Female mice with an XY sex chromosome complement develop severe angiotensin II-induced abdominal aortic aneurysms. (2017).

Sex-specific autosomal gene expression

- Genes encoding AT2R and ACE2 are located on the X chromosome; thus, increased dosage of these genes may contribute to the relative cardioprotection in females.

- Differences in genotype frequencies of X chromosome-linked polymorphic alleles between males and females are likely to contribute to sex differences in physiology and pathophysiology.

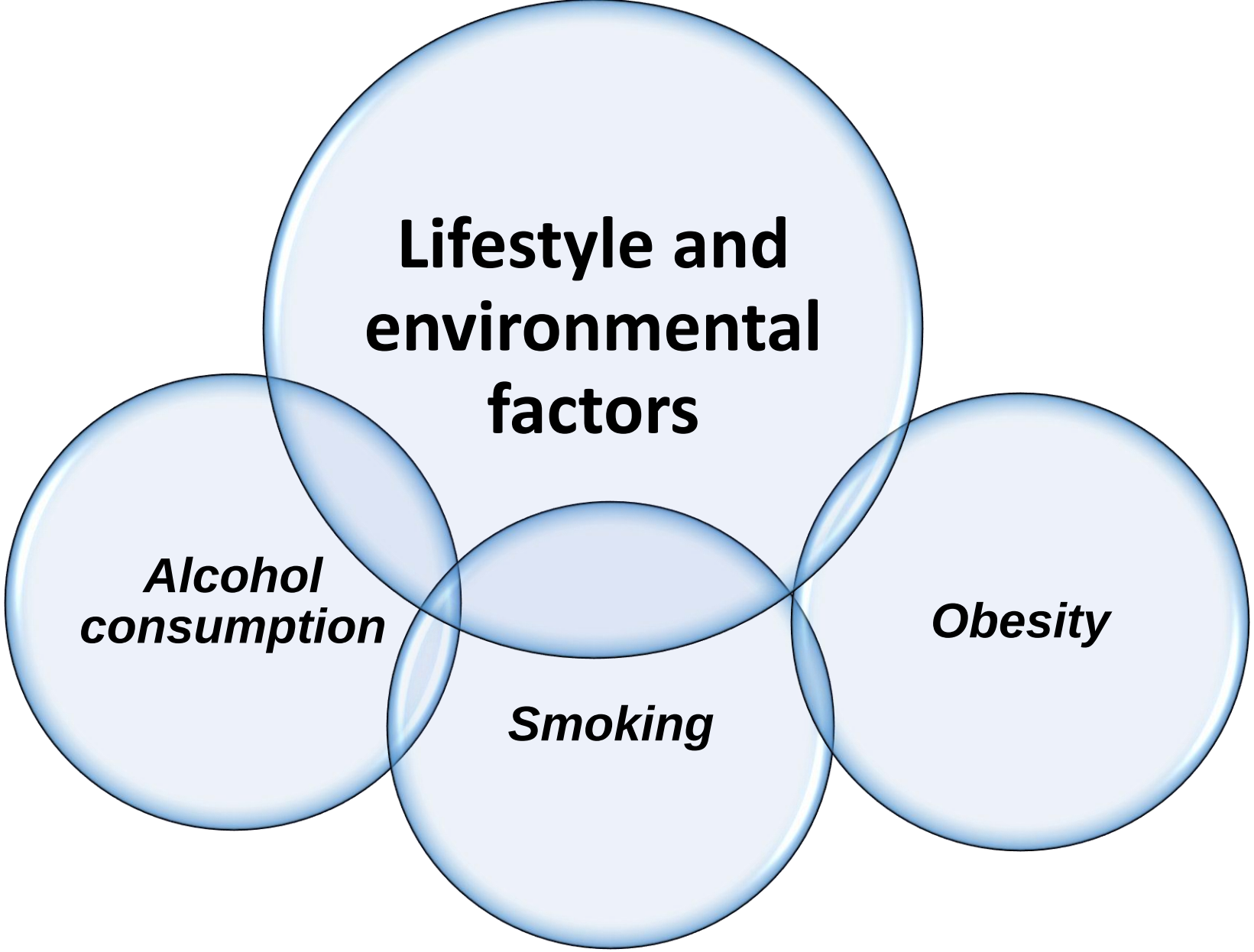
Immune system

- Sex differences in renal T cell subpopulations have also been reported in spontaneously hypertension:

  - Females have more anti-inflammatory Treg cells,
  - Males have more pro-inflammatory T helper 17 (TH17) cells

- Sex differences in T cells are observed in humans:

  - CD4+ T cells from women produce more IFNγ, a marker of an anti-inflammatory phenotype
  - CD4+ T cells from men produce more IL-17, a pro-inflammatory marker, suggesting that sex differences exist in the CD4+ T cell subpopulations.


Lifestyle and environmental factors
Alcohol consumption
Smoking
Obesity

Alcohol consumption

- Moderate to high levels (3–4 or more alcoholic drinks per day) have been associated with increased risk of CVD

- Although alcohol consumption is in general lower in women than in men, those women with moderate to high alcohol consumption have an increased CVD risk compared with men.

Walker, R. K. *et al.* The good, the bad, and the ugly with alcohol use and abuse on the heart. *Alcohol Clin. Exp. Res.* **37**, 1253–1260 (2013).

Smoking

- Smoking is associated with a greater risk of coronary heart disease in women than in men
- Greater risk of stroke in women than in men
- Smoking has been associated with an increase in testosterone levels in men and women
- Oestrogen deficiency in women and to bring forward the onset of menopause

Zhao, J., Leung, J. Y., Lin, S. L. & Schooling, C. M. Cigarette smoking and testosterone in men and women: A systematic review and meta-analysis of observational studies. *Prev. Med.* **85**, 1–10 (2016).

Obesity

- Obese premenopausal women have a threefold higher risk of hypertension than lean women
- comparable increase in BMI causes a greater increase in systolic BP in women than in men
- obese women also develop more obesity-related conditions — such as hyperlipidaemia, insulin resistance and T2DM — than obese men, and these conditions are associated with more severe outcomes in women
- obese women have disproportionately high levels of plasma aldosterone compared with the levels in obese men

Lambert, E. *et al.* Gender differences in sympathetic nervous activity: influence of body mass and blood pressure. *J. Hypertens.* **25**, 1411–1419 (2007).

The key factors in the treatment of HTN whith attention to the sex-specific diffrences

- Sex differences in BP control and responses to treatment are present at all stages of life, and understanding these differences may improve treatment in both men and women .

- Age and body mass index have been much stronger prediction of incident hypertension than gender in epidemiologic studies.

- Drug treatment of hypertension has roughly the same benefits for woman and men

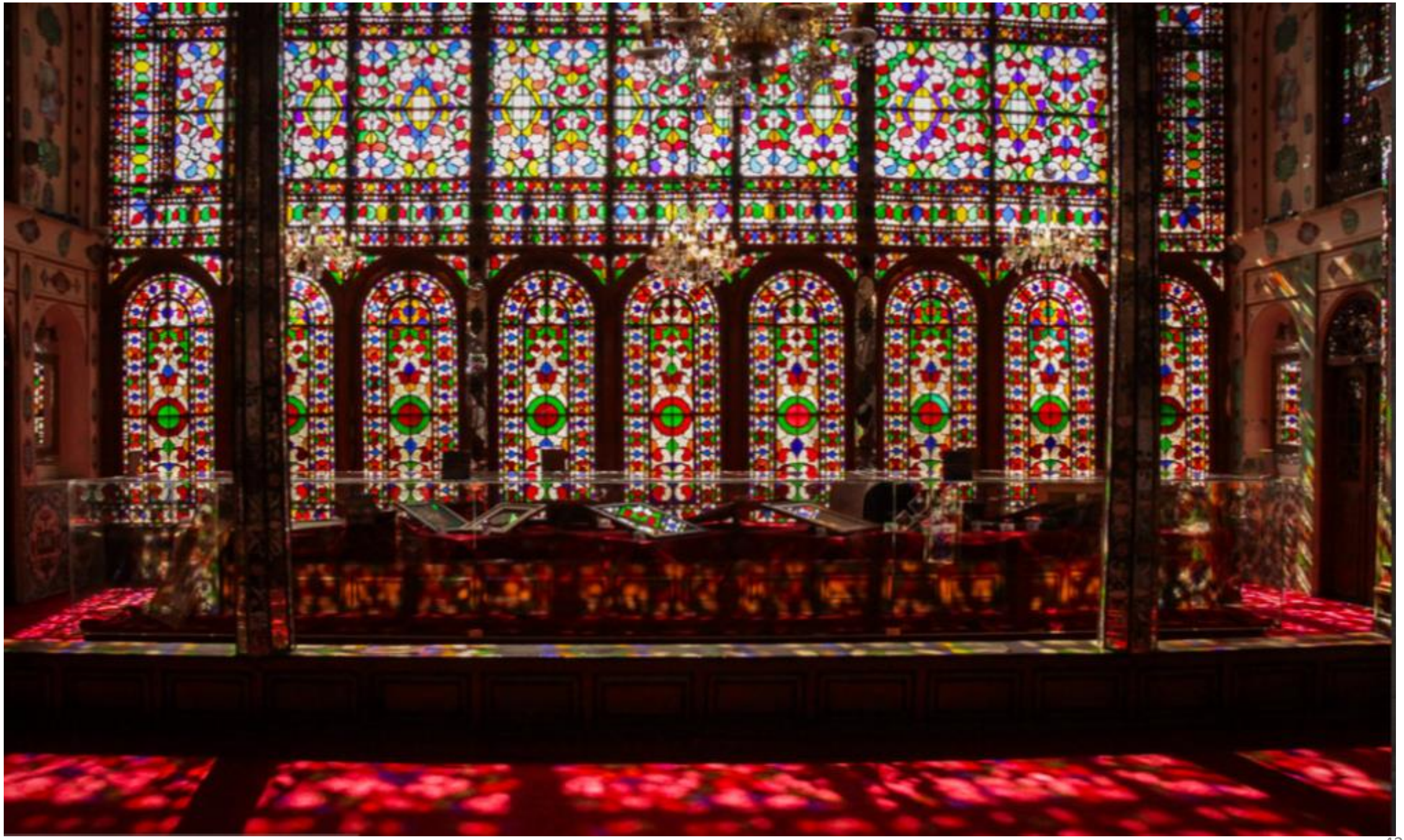
Brener & rector’s the kidney text book, edition 10

- Women do not respond to treatment as well and have a higher risk of death following a cardiovascular event.

- Angiotensin II-mediated reduction in renal blood flow is inhibited at a lower dose of the angiotensin receptor blocker (ARB) in women than in men.

- AT2R activation has been reported to stimulate the conversion of androgen to oestrogen in the ovary.

- Targeting AT2R signalling may be beneficial for ameliorating the detrimental effects of PCOS on vascular health.



THANK YOU